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COVID-19 Monoclonal Antibodies: Feasible Mechanisms for Generating Needed Evidence

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COVID-19 Monoclonal Antibodies:
Feasible Mechanisms for Generating Needed Evidence

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This Duke-Margolis resource on COVID-19 response policies is intended to inform and help guide policy makers addressing the evolving COVID-19 pandemic in the United States and around the globe, and will be updated as the pandemic and response capabilities change over time.

It contains recommendations for a U.S. Federal response as well as steps and resources for stakeholders across the health care ecosystem. We will add further resources to address a range of related, critical policy challenges.

We thank our many collaborators, co-authors, and reviewers who have contributed significant expertise and guidance on these rapidly evolving issues. Please reach out to us with additional suggestions for resources and effective policies at dukemargolis@duke.edu - we welcome your input.

Executive Summary

Monoclonal antibody (mAb) treatments for COVID-19 have been approved for emergency use, but there are several challenges to effective access for patients who may benefit. Especially with limited supplies, better evidence is urgently needed on the effectiveness of COVID-19 antibodies across different models of providing the treatment (e.g., in infusion facilities or at home), patient groups that may differ in benefits and risks, and other characteristics of treatment administration (e.g., optimal antibody dose, timing of administration, etc.). This report outlines the key evidence questions that need to be answered, the core data elements that could help to answer them, and potential approaches to rapidly adapt available evidence development platforms to provide evidence that enables greater health impact of these new treatments. The following actions will enable this evidence development to occur:

- Implement a collaboration with support from the Federal government, manufacturers, and/or payers to rapidly adapt existing COVID-19 registries and data platforms to support evidence development, in coordination with ongoing clinical trials
- Conduct shared analyses to develop evidence on questions related to effective antibody allocation, and on innovative models for antibody administration especially for underserved populations
- Use this evidence to support further guidance to health care organizations, payers, and Federal and state policy makers to optimize use of antibody treatments

Introduction

Promising initial evidence from monoclonal antibody (mAb) clinical trials has led to two emergency use authorizations (EUAs) for broad categories of patients at high risk for COVID-19 complications and hospitalizations: Eli Lilly's bamlanivimab, which has been estimated to reduce patient hospitalization rates from 10% to 3% in the EUA; and Regeneron's combination antibody casirivimab and indevimab, which has been estimated to reduce hospitalization rates from 9% to 3%. While the evidence is limited, the available trials suggest larger risk reduction in patients at higher risk.

A new care model is needed for early management of COVID-19 patients to use these antibodies effectively, to help patients in high-risk groups (over 65, obese, and/or having significant comorbidities) receive timely testing and referral for antibody infusion. Treatment is not effective in patients who have progressed to requiring oxygen or hospitalization. There are near-term challenges related to identifying those patients likely to benefit most and providing infusions, either at a dedicated hospital or ambulatory facility or through home or mobile infusion providers (e.g., in nursing homes, rural areas, and for other patients who may not be able to travel readily to a COVID-19 infusion center).

As infusion capacity increases, shortages are likely – with around 1 million doses of the Eli Lilly product and 300,000 doses of the Regeneron product available through January. Consequently, there are urgent evidence issues to address:

- Since the vast majority of COVID-19 patients, even those at relatively high risk, recover without serious complications, is it possible to refine risk prediction models to target the limited supply of antibodies more effectively?
- Since the clinical trials that were the basis for the EUAs included only a limited number of events, is it possible to augment the currently ongoing and planned clinical trials (e.g., on dosing) by implementing additional simple trials in the context of real-world use?
- What are the most effective models for delivering and paying for antibody treatment, with equitable and efficient access?

Health care systems, payers, patients, and the Federal government all have a shared interest in developing this evidence. This issue brief outlines key questions around the most effective use of antibodies, the data elements that are likely necessary for answering them, and potential approaches for initiating a broad-based evidence generation effort

Key Questions for Further Evidence Development

A range of key evidence questions related to the effectiveness of COVID-19 antibodies have not been adequately addressed. **Such evidence could further refine patient risk stratification and prioritization, improve access and administration strategies, and support more effective use of**

combinations of therapies for early-stage treatment and prevention of COVID-19. Additional clinical trials are underway to address these issues, but such studies are limited. Some of this evidence could be developed through observational studies, but additional opportunities to randomize patients would also be helpful to augment evidence on the effectiveness of antibodies.

Some questions related to *clinical benefit-risk assessment* can be addressed by tracking populations of higher-risk COVID-19 outpatients, or patients who receive antibodies:

- **Better differentiation of risk of hospitalization:** What are the relative risks of subgroups of patients 65+, obese, and/or with significant comorbidities, and are there additional readily measurable predictors of risk of progression (e.g. viral concentration on diagnostic tests, presence of antibodies)?
- **Safety:** What is the rate of occurrence of rare but serious adverse events not related to COVID-19 progression (allergic reactions, other)?

Additional questions related to *effectiveness* of antibodies would ideally be addressed through clinical trials, including practical real-world trials, and potentially through methods that involve matched comparisons if such randomization is not feasible:

- **Effectiveness:** Are the initial randomized trials replicable, and is the impact of antibody treatment on outcomes proportional to risk of hospitalization?
- **Optimal dosing:** Are current doses too high (or too low) for effectiveness in many patients?
- Impact of timing: How does antibody effectiveness decline over time since infection or symptoms; does delaying treatment in patients with mild symptoms until they progress lead to worse outcomes?
- **Comparative effectiveness:** When available, do alternative products have different effects? How much better are combination antibodies than single antibodies? Are antibodies beneficial in patients who have been vaccinated or received other treatments?

Another set of questions pertains to evidence that could guide the further development of *care models for effectively administering antibodies*:

- **Costs and safety:** Are there differences in the costs and safety events associated with alternative models for antibody delivery (e.g., hospital-based, ambulatory center-based, mobile or home)?
- **Access:** What are the implications of alternative models for access for particular high-risk patients (e.g., frail elderly/homebound, skilled nursing facility or alternative living facility, patients in underserved areas)?

Finally, antibodies are being assessed in additional populations, in particular for post-exposure prophylaxis or other prophylactic uses in people at high risk of COVID-19 complications.

Core and Supplemental Data for Evidence Development

Addressing these priority evidence questions will require timely and reliable collection of consistent data, ideally from populations of patients who may or may not receive antibody treatment. **To encourage the capacity to scale and integrate patient experience, these data should encompass a minimum set of elements with a high degree of reliability.** Such a core dataset could include:

- **Key patient characteristics:** demographics; major comorbid conditions; presence of major symptom types and duration; time since testing and diagnosis; time since exposure (if known)
- **Key diagnostic test results:** viral concentration in nasal swab (Ct), viral load or antibody levels in blood samples (not routinely collected)
- **Specific antibody and dosage used**
- **Timing of administration** relative to onset of symptoms and/or testing
- **Occurrence of acute infusion reaction** or complication
- **Key outcomes**, including occurrence of subsequent ED use and/or hospitalization, and potentially other major clinical complications, including need for ICU care and death

Organizations participating in evidence generation activities will need to clarify where specific data elements should be sourced. Some data may be captured at the time of antibody infusion, either from electronic clinical data systems or (if not too burdensome) from provider reporting. Other key information (e.g., data on hospital and emergency department utilization) may be obtained from payer claims databases. Data might also be obtained from patient reports or other sources. Putting together such data at scale may be easiest for large integrated health systems.

Many health systems or collaboratives may be able to produce additional data beyond this core set – for example, additional laboratory tests, concomitant medication use and symptom status updates – enabling supplemental analyses, but the potential burden of data collection may limit the ability of organizations to participate in more complex efforts.

Efforts to develop a common data platform should focus on efficiency and parsimony in data collection, through such steps as developing tools for capturing data from electronic medical records and identifying the most promising additional data elements for improving evidence. This will enable participation of more health care providers and systems, particularly in situations where COVID-19 cases may be surging and health care providers and systems are stressed. Incremental payments for data collection could also help to overcome some of these barriers to

increased participation by providing financial support to enable participation even under difficult scenarios.

Potential Platforms and Methods for Developing Better Evidence

There are a range of platform approaches that could develop and use the core key data elements described above to answer evidence questions. These include:

- **Analysis of health system COVID-19 registries:** Some integrated delivery system networks and hospital networks have already developed COVID-19 patient registries, which generally include data on patient characteristics and clinical information for outpatients after diagnosis with SARS-CoV2 infection. For example, UnitedHealth Group (UHG) and OptumHealth have partnered with Eli Lilly to assess utilization and associated outcomes of bamlanivimab treatment in UHG's large Medicare Advantage population. The trial will pilot in-home testing and in-home infusion, and will include comparisons of treated patients against matched patients who are not treated. Some data and technology companies have also independently developed registries using data integrated across multiple sites that could be adapted for antibody-related studies. To support priority analyses, the participating registries should be able to track patients from infusion (or diagnosis) through major subsequent events during the course of their infection, which may require linking data from the infusion setting to subsequent hospital use data (e.g., from lined insurance claims). As noted above, they should also include data from the population from which infused patients were selected. Parallel analyses could then be run on these registries, with a central protocol and coordinating body organizing joint the joint effort. For example, the FDA and Reagan-Udall Foundation's Evidence Accelerator used a platform protocol developed by Duke-Margolis to support similar analyses of remdesivir distribution and use, with support from MITRE and a range of data and analytic partners.
- **COVID-19 antibody network or multicenter registry:** If supporting software and infrastructure can be provided quickly, multiple existing registries that meet minimum data and data characterization standards could be linked to allow direct, larger-scale analysis. An intermediate step toward integration could be the conduct of distributed or federated analysis protocols run consistently by each registry participating in the network. Examples in the COVID-19 context include the multicenter convalescent plasma registry supported by the Mayo Clinic in collaboration with other health systems, or the PCORnet HERO registry, which captures data on health care workers in multiple health systems.
- **Single- or multi-payer supported registry:** Because of the potential for health and cost benefits from improved evidence on antibodies, payers may also support the development of registries. Such a payer-supported registry could be maintained by the payer or by an independent group supported by a consortium of payers. Alternatively,

payers including CMS could collaborate to support independent registries, potentially in collaboration with manufacturers.

- **Simple clinical trial capacity:** Building on a consistent data collection and analysis capacity, a registry system could provide a network of sites to conduct simple clinical trials that augment trials currently underway using more detailed protocols. Such trials would need to be easy to implement, using straightforward protocols and avoiding features like placebo arms that may be difficult to incorporate into routine clinical practice. Feasible questions might include dosing or timing of administration. This approach would likely require an NIH- and FDA-endorsed protocol, a straightforward central IRB process, support for timely informed consent, minimal additional data collection burden, and other steps to ease participation.

- **Learning network and regional analysis for effective implementation:** Antibody administration requires new models of care to assure timely diagnostic testing and timely referral of appropriate high-risk COVID-19 patients to a specialized infusion provider – or bringing mobile or home infusion capacity to the patient. While some hospitals and health systems have begun setting up infusion capacity, more evidence is needed on the best models of care for particular types of patients and communities. A "learning network" to exchange ideas and promising practices for prioritization, referral, and infusion – particularly focusing on challenging populations like those in nursing homes, rural areas, and underserved communities – could help identify effective approaches and assure that payments and other supporting policies are being implemented in a way that supports their expansion. Regional analyses in collaboration with state or local governments could identify ways to optimize antibody access for whole populations.

Advancing Evidence Development for Monoclonal Antibodies

Efforts to develop relevant evidence must occur in a timely way to support more effective use of antibodies. Building on these existing systems, limited funding from the Federal government (through Operation Warp Speed or NIH) or manufacturers would help sustain these activities.

Observational analyses are likely to be easiest to conduct, and are well suited to descriptive studies. If antibody benefits are roughly proportional to patient risk of hospitalization, as suggested in the clinical trials used as the basis for the EUAs, refining predictive models for hospitalization risk could substantially enhance the impact of the limited current supply of antibodies. Many organizations are currently using or adapting the Cleveland Clinic's predictive model of hospitalization risk. Refining this or similar models to identify additional, readily observable or measurable patient factors that further refine risk prediction could significantly improve the number needed to treat to prevent a hospitalization. Given the limited number of clinical trials, clinical experts have raised concerns about quantifying the risk of serious adverse events like allergic reactions in antibody-treated patients. Registries could provide evidence to better define these risks and help assure safety. Such studies could also help characterize access

issues (are similar patients in certain demographic or geographic groups more or less likely to be treated?) and associated resource use in the emerging antibody care models.

These studies could be conducted through a "collaboratory" or integrated registry, or a network of organizations conducting parallel analyses using consistent data and methods. As an initial step, potential collaborators could agree on a common or federated data platform and priority questions and methods, and share their own analyses. This approach has been utilized successfully by the FDA and Reagan-Udall Foundation's COVID-19 Evidence Accelerator. It could be expanded with additional technical support, for example from MITRE, academic sponsors of COVID-19 research networks like Mayo or PCORnet, or partnerships with data technology companies.

Such analyses could potentially incorporate assessments of **pilots of innovative care models** aiming to improve antibody access for challenging populations. In collaboration with state and local public health leaders, the pilots could inform the implementation of state and regional plans for optimizing the use of antibodies.

The resulting evidence development system could also augment ongoing trials that seek to address remaining gaps in evidence on antibody effectiveness. Observational studies are limited by potential biases in unmeasured patient characteristics or associated treatments. However, considerable research has helped assess such biases. Moreover, the limited availability of antibodies may permit comparisons of similar populations that at least temporarily differ in access – for example, patients located near infusion centers versus those that are not, or a before/after comparison (potentially with a preidentified control population) when a new antibody care model opens or additional antibody supply becomes available.

A rapidly emerging antibody evidence collaboration could also potentially house modules of **large, simple randomized trials** in which patients at some participating organizations are randomized to alternative antibody treatment protocols that are viewed as having clinical equipoise. Such alternatives might include questions about the effectiveness of alternative doses, timing of administration (e.g., does a day or two of observation for patients with mild or limited symptoms help differentiate whether or not the patient will benefit from antibody administration), and other questions related to the comparative effectiveness of alternative strategies for using these treatments. Placebo controls may not be feasible or ethical in these simple trial approaches.

Next Steps

Antibodies are a potentially valuable therapy available in the near term for patients at risk of progressing to hospitalization or death from COVID-19, and in the future for those that may not have been vaccinated or did not respond to vaccination. But both the supply of antibodies and

evidence on how to use them effectively is limited. Through timely action to build on existing data collection and analysis opportunities, especially involving health systems and data technology companies, these evidence gaps can be addressed now:

- Implement a collaboration with support from the Federal government, manufacturers, and/or payers to rapidly adapt existing COVID-19 registries and data platforms to support evidence development, in coordination with ongoing clinical trials
- Conduct shared analyses to develop evidence on questions related to effective antibody allocation, and on innovative models for antibody administration especially for underserved populations
- Use this evidence to support further guidance to health care organizations, payers, and Federal and state policymakers to optimize use of antibody treatments